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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/383,894	08/26/1999	MING LI	004.00191	7158

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	PAPER NUMBER
1635	18

DATE MAILED: 02/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/383,894	LI, MING	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *16 March 2001* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The request filed on November 25, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/383,894 is acceptable and a CPA has been established. An action on the CPA follows.

Drawings

The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on March 16, 2001 have been approved. A proper drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The correction to the drawings will not be held in abeyance (see 37 CFR 1.85(a)).

In order to avoid abandonment, the drawing informalities noted in Paper No. 6, mailed on September 12, 2000, must now be corrected. Correction can only be effected in the manner set forth in the above noted paper. A copy of the Draft's person's review, originally mailed with the Office action mailed September 12, 2001, is attached hereto. The correction to the drawings will not be held in abeyance (see 37 CFR 1.85(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-49 are maintained as rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the prior Office action (mailed 09-12-00), because the specification, while being enabling for modifying beta cell insulin secretion using known calcium channel blockers, does not reasonably provide enablement for modifying beta cell insulin secretion using any calcium channel blocker or inhibitor of channel formation, ribozyme, antisense or an expressed gene *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection of record is set forth as follows.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 43-49 are drawn broadly to methods of modulating insulin secretion in pancreatic beta cells by modifying levels of functional T-type calcium channels by any mechanism, including modulating insulin secretion *in vivo* (whole organism). Claims 43-46 are further drawn

to modifying levels of functional T-type calcium channels using antisense or expressing a nucleic acid encoding a T-type calcium channel in any setting, including *in vivo* (whole organism).

The specification provides examples wherein T-type calcium channel blockers, including mibefradil and $NiCl_2$ are administered to pancreatic cells, *in vitro* (cell culture) and T-type calcium channel activity is blocked. There are no examples provided in the instant specification wherein an inhibitor of channel formation, an antisense molecule, a ribozyme or an expressed pancreatic T-type calcium channel are demonstrated to alter insulin secretion in beta cells in any setting, including *in vitro*. Further, there are no examples provided by the instant specification wherein an antisense molecule or a ribozyme are demonstrated to alter the level of a T-type calcium channel or alter the expression of a nucleic acid encoding a T-type calcium channel in any setting, including *in vitro*.

At the time the instant invention was made, modifying insulin secretion in beta cells in vivo (whole organism) via calcium channel blockers was unpredictable (see for example Verma, S. et al. page 126), calcium channel blockers reported to inhibit insulin secretion *in vitro* do not predictably produce the same effect *in vivo*. The reason for this variability was unknown, and one skilled in the art would not be able to predict what calcium channel blockers would modify insulin secretion *in vivo* (whole organism), based on *in vitro* screening.

Further, the claimed methods read on *in vivo* (whole organism) methods of modifying insulin secretion using nucleic acid based drugs, including antisense, ribozymes and gene therapy methods. At the time the instant invention was made, and even now, *in vivo* (whole organism)

methods using antisense, ribozymes and gene therapy were highly unpredictable (see, for example, Branch, Agrawal, Rossi, Anderson and Verma, I. et al.) due to issues including the determination of accessible target regions, how to specifically deliver an antisense molecule, ribozyme or gene therapy vector to a target cell at a concentration effective to result in a desired effect, and, in the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene.

The specification, as filed, provides only general guidance with regard to such factors. Due to the unpredictability in the art, the field to date does not have guidelines which would enable one skilled in the art to routinely practice methods drawn to *in vivo* applications of antisense, ribozymes and gene therapy. As such, one skilled in the art would need to determine such factors de novo, through empirical, undue trial and error experimentation. The skilled artisan would need to first determine what compounds interfere with T-type calcium channel pore formation and what ribozyme and antisense sequences are able to inhibit the expression of a nucleic acid encoding a pancreatic T-type calcium channel, *in vivo* or *in vitro*. Further, one skilled in the art would need to determine which of these compounds change the level of functional t-type calcium channels in a manner and to the degree that insulin secretion would be modified. Additionally, one skilled in the art would need to determine how to deliver antisense molecules, ribozymes or gene therapy vectors specifically to pancreatic beta cells, in vivo, at a concentration which is effective to change the level of functional t-type calcium channels, and modify insulin secretion in said beta cells. This would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half

life and stability of the antisense or ribozyme molecule *in vivo*. For gene therapy, in particular, it would require the determination of an appropriate vector and enhancer-promoter combination for beta-cells "the search for such combinations is a case of trial and error for a given type of cell."(see Verma, for example p 240, columns 2 and 3) in order to get a high and sustained expression of a t-type calcium channel, such that beta cell insulin secretion would be modified.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance by the inventor, the lack of working examples, and the quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43 and 47 are maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Verma, S. et al. for the reasons of record set forth in the prior Office action (mailed 09-12-00). The rejection of record is set forth as follows.

Verma, S. et al. disclose a method wherein hypertensive rats are administered mibefradil, a T-type calcium channel blocker, with a resultant decrease in insulin secretion, which would necessarily be a decrease in insulin secretion by the rat beta cells.

Therefore, Verma et al. anticipates claims 43 and 47.

Claims 43 and 47 are maintained as rejected under 35 U.S.C. 102(a) as being anticipated by Bhattacharjee et al. for the reasons of record set forth in the prior Office action (mailed 09-12-00). The rejection of record is set forth as follows.

Bhattacharjee et al. disclose a method wherein rat beta cells (INS-1) are contacted *in vitro* (cell culture) with $NiCl_2$, with a dose dependent reduction in glucose stimulated insulin secretion.

Therefore, Bhattacharjee et al. anticipates claims 43 and 47.

Claim 43 is maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Kato et al. for the reasons of record set forth in the prior Office action (mailed 09-12-00). The rejection of record is set forth is set forth as follows.

Kato et al. disclose a method wherein neonatal rats are treated with streptozocin, increasing the level of functional T-type calcium channels, evidenced by the increased Ba^{2+} induced currents, and increasing insulin secretion.

Therefore Kato et al. anticipates claim 43.

Response to Arguments

Applicant has not provided any new arguments to traverse the rejections of record.

Conclusion

Any rejection of record not repeated herein is considered to be withdrawn.

This is a CPA of applicant's earlier Application No. 09/383,894. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703)308-7523. The Examiner can normally be reached Monday-Thursday from 8:30 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
February 3, 2003

KAREN LACOURCIERE
PATENT EXAMINER